

REVIEW ARTICLE

Ultradian rhythms in pituitary and adrenal hormones: their relations to sleep

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Sleep and circadian rhythmicity both influence the 24-h profiles of the main pituitary and adrenal hormones. From studies using experimental strategies including complete and partial sleep deprivation, acute and chronic shifts in the sleep period, or complete sleep-wake reversal as occurs with transmeridian travel or shift-work, it appears that prolactin (PRL) and growth hormone (GH) profiles are mainly sleep related, while cortisol profile is mainly controlled by the circadian clock with a weak influence of sleep processes. Thyrotropin (TSH) profile is under the dual influence of sleep and circadian rhythmicity. Recent studies, in which we used spectral analysis of sleep electroencephalogram (EEG) rather than visual scoring of sleep stages, have evaluated the temporal associations between pulsatile hormonal release and the variations in sleep EEG activity. Pulses in PRL and in GH are positively linked to increases in delta wave activity, whereas TSH and cortisol pulses are related to decreases in delta wave activity. It is yet not clear whether sleep influences endocrine secretion, or conversely, whether hormone secretion affects sleep structure. These well-defined relationships raise the question of their physiological significance and of their clinical implications.

Key words: Prolactin, growth hormone, thyrotropin, cortisol, sleep EEG, spectral analysis, delta wave activity, ultradian rhythm, pulsatility

Introduction

The plasma concentrations of most hormones are known to fluctuate in a pulsatile manner. In recent years, it has been shown that numerous 24-h endocrine rhythms arise from a succession of secretory pulses of various magnitude and frequency rather than from continuous release with superimposed fluctuations [1]. The temporal organization of the pulses within 24 hours reflects both endogenous and exogenous inputs. Some of the 24-h rhythms depend on a circadian biological clock, located in the suprachiasmatic nuclei of the hypothalamus, while others are influenced by sleep-related or environmental factors, such as the sleep-wake cycle and feeding habits. The way in which the sleep-wake cycle interacts with an endocrine rhythm has been

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described as falling into three groups: (1) hormones poorly influenced by sleep such as ACTH, cortisol and melatonin, (2) hormones strongly influenced by sleep on the whole such as prolactin (PRL) and thyrotropin (TSH); (3) hormones influenced by a particular stage of sleep, such as growth hormone which is linked to the first SWS episode occurring at the beginning of the night [2]. In recent years, experimental evidence has been accumulated concerning the temporal organization of the secretory pulses within the 24 h period, and some well-defined endocrine ultradian rhythms, i.e. with a period shorter than 24 h, have been identified. Then, it was shown that the hormone pulses could be modulated both by the circadian clock and the sleep processes which interact in a specific manner, depending on the hormone, to provide the overall profiles within the 24-h period.

A variety of methods have been used to investigate sleep-hormone relationships, including: complete and partial sleep deprivation, acute or chronic shifts of the sleep time or complete sleep-wake reversal as occurs with transmeridian travel or shift-work, administration of pharmacological agents which disturb either sleep or hormone secretion, and finally the study of specific pathologies which manifest either endocrine or sleep disturbances. This paper presents current knowledge of the influence of sleep as a whole on the main pituitary and adrenal hormones, namely PRL, GH, TSH and cortisol. It presents new findings from recent studies in which spectral analysis of the sleep electroencephalographic (EEG) activity and new analytical procedures were used to determine the dynamic oscillatory pattern of EEG activity in the different frequency bands and their associations with hormonal pulses. Finally, special attention is given to the mechanisms responsible for the pulsatile activities of both endocrine secretion and sleep EEG, and for their concomitances.

Analytical Procedures

Sleep data

Polygraphic recordings and spectral analysis

Sleep recordings were performed using four EEG derivations (F_3 , C_3 and P_3 versus A_2 , and C_4 versus A_1), one chin electromyographic derivation and one diagonal electrooculographic derivation (upper canthus of one eye versus lower canthus of the other eye). The recordings were visually scored at 30-s intervals and sleep stage scoring was conducted using standardized criteria of Rechtschaffen and Kales. However, to describe the sleep EEG as a series of discrete stages can be misleading, because it tends to obscure the fact that sleep is a continuous, oscillatory process. Spectral analysis of the sleep EEG, based on Fast Fourier Transformation (FFT), allows for a more detailed and dynamic description of the sleep processes than visual sleep stage scoring and for a quantitative analysis of the sleep EEG [3]. For all-night spectral analysis, the EEG signal was converted from analogue to digital with a sampling frequency of 128 Hz. Subsequently, spectra were computed for consecutive 2-s periods using a FFT-algorithm and the values for 15 consecutive 2-s periods were averaged to yield power density values for 30-s periods. Moreover, in order to study concomitant variations of sleep EEG activity and hormonal release, the power density values were smoothed with a median filter of 20 points in order to obtain one point every 10-min corresponding to the hormone measurements in blood sampled at 10-min intervals. The spectral parameters studied were power densities in absolute and relative power [percentage

of the global EEG band (0.5–35 Hz)] for delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz) and beta (13–35 Hz). In addition, the alpha slow-wave index (ASI), a good indicator of intra-sleep awakenings, was analysed ($ASI = \text{alpha} / (\text{delta} + \text{theta})$) [4]. Particular attention was focused on the delta wave activity, used as an indicator of sleep depth.

Determination of delta wave peaks

For quantification and characterization of the main delta wave peaks, the individual profiles were analysed by a modification of the pulse analysis algorithm ULTRA [5]. Taking into account the large inter-individual variability in the levels of the delta wave activity, identification of the main peaks was achieved using a subject-adapted threshold for detection. This threshold was set at 20% of the maximum increment in delta wave activity observed in the subject. A peak was considered significant if both the increase and the decrease exceeded this threshold. For each significant peak, the time of occurrence of the maximum was determined.

Hormonal data

Blood sampling and plasma hormone

Four hours before the beginning of the recordings (in order to avoid a venipuncture-related stress), a catheter was inserted under local anaesthesia into an antecubital vein, which was kept patent with a heparin-containing solution. Blood was sampled continuously using a peristaltic pump and collected in an adjoining room over 10-min periods. A maximum of 250 ml blood was removed during the experiments, this produced no modification of haematocrit, and of hypovolaemia-responding systems. Plasma hormones were measured by radio-immunoassay using commercial kits. All samples from a given subject were analysed in the same assay.

Deconvolution of hormonal levels

The deconvolution procedure allows the calculation of hormone secretory rates from plasma concentrations using a mathematical model that removes the effects of hormonal distribution and degradation. Thus, this procedure provides a more accurate estimation of the secretory process than peripheral concentrations, and allows for a more precise evaluation of the temporal concordance between hormonal secretion and EEG events.

The individual hormonal profiles were analysed and significant pulses were identified using a modification of the pulse detection algorithm ULTRA [5]. The statistical error propagation of the uncertainty in data measurements was taken into account in the determination of the secretory profile. An increase in the secretory rates was considered to be significant when the sum of the standard deviations associated with the successive estimated secretory rates was exceeded. Significant decreases were similarly identified. Thus, a secretory pulse was considered significant if both its increment and its decrement exceeded significant differences in secretory rates. For each significant pulse, the time of occurrence of the maximum level, the ascending phase, the descending phase, and the total duration were determined. For TSH, taking into account the fact that a considerable part of its secretion is tonic, the secretory rates were not determined, and the significant peaks of plasma concentration were determined using ULTRA [5].

Analysis of temporal relationship between hormonal profiles and EEG activity

Cross-correlation analysis

The temporal relationship between the hormonal and the EEG activity profiles was quantified using cross-correlation analysis. Cross-correlation coefficients were computed for lags $[-3]$, $[-2]$, $[-1]$, $[0]$, $[+1]$, $[+2]$ and $[+3]$ between the two chronological series, each lag corresponding to a 10-min blood sampling interval. Cross-correlation analysis assesses the tendency of two time series to covary in the same or opposite directions simultaneously with either a positive or negative lag, and thus estimates the overall coordinate behaviour of the two series. This analysis is not adapted to estimating temporal links between discrete events occurring in the series such as the pulses of GH secretion and the peaks of delta wave activity. Indeed, a large concomitant pulse in the two series strongly influences the correlation, masking the effect of non-synchronized small peaks, even if they are more numerous. Thus it is an interesting tool for estimating the overall relationship between two parameters; however, taking into account the limitations of this analytical method, accurate temporal links between pulsatile events need to be further assessed by other methods, such as pulse by pulse analysis with calculation of mean pulses.

Mean pulses of hormonal and EEG activities

Following pulse detection of hormones and delta wave activity, a mean pulse was calculated for each parameter. For each subject, all individual pulses were aligned by their maximum and were averaged point by point, $[-4]$, $[-3]$, $[-2]$, $[-1]$ points before the maximum value $[0]$, and $[+1]$, $[+2]$, $[+3]$, $[+4]$ points after the maximum of the hormonal pulse. In order to obtain a mean pulse for the whole group of subjects, and in order to reduce the inter-individual variability, the 10 individual mean pulses were expressed as percentages of the individual mean, and averaged point by point. Concomitant delta wave activity was similarly expressed, and the parameters were plotted together. This analysis provides an illustration of the temporal relationships between hormonal pulses and concomitant variations in EEG activity.

Relationships between sleep and hormonal profiles

Sleep and EEG rhythms

Three basic processes underlie sleep regulation: (1) a homeostatic process mediating the rise in "sleep pressure" during waking and the dissipation of "sleep pressure" during sleep; (2) a circadian process, a clock-linked mechanism, independent of prior sleep and waking; (3) and an ultradian process occurring within sleep and represented by the alternance of non-rapid eye movement (NREM)–REM sleep cycles [6].

Proceeding from desynchronized EEG activity during wake, the cortical electrical activities become synchronized after sleep onset. Within sleep, the alternation of NREM–REM cycles, are evidenced by the alternation of slow and rapid EEG activities. The slow wave activity or delta wave activity (0.5–4 Hz) with high-amplitude oscillations, mainly observed in deep sleep (stages 3–4), reveals a state of synchronized brain activities. It has been reported that the rhythmic activity of delta waves is generated in the cerebral cortex, with an important role played by the thalamus as well [7]. The hypothalamic paraventricular nucleus (PVN), responsible for CRH release

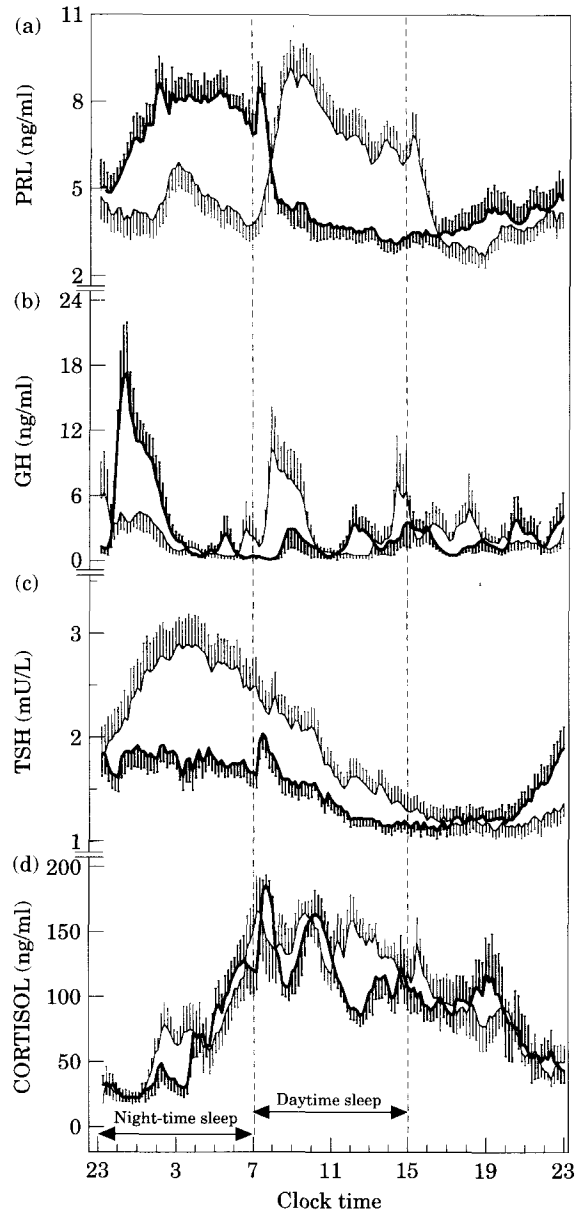


Figure 1. Effect of an 8-h shift in the sleep period on the mean (\pm SE) 24-h profiles of plasma prolactin (PRL) (a), growth hormone (GH) (b), thyrotropin (TSH) (c) and cortisol (d).

and for inhibition of GHRH release, can play an important role in the production of REM sleep and in the generation of its ultradian rhythm. Thus, it could be directly or indirectly responsible for the inhibition of the slow wave generation, and concomitantly for GH release.

Prolactin (PRL)

Under baseline conditions, the 24-h profiles of PRL show low levels during daytime and high levels during nocturnal sleep. Studies using naps or shifts of the sleep period have demonstrated a close association between sleep and the increase in PRL release [8]. Sleep onset, irrespective of the time of day, was described to have a stimulatory influence on PRL release.

Figure 1 illustrates the effect of an 8-h shift in the sleep period on the 24-h PRL profiles in eight subjects. In order to differentiate circadian influences from sleep-related effects, the subjects were studied once during a normal 24-h sleep-wake cycle with sleep from 2300 to 0700h, and once during a 24-h cycle with an abrupt sleep shift consisting in an 8-h delay in the sleep period (from 0700 to 1500h). The nocturnal increase of PRL was immediately displaced by the acute sleep shift, indicating the strong influence of sleep processes on its release [9]. However, a significant PRL pulse was found in all subjects during the night on which sleep was deprived, at the time of habitual sleep. This pulse was also observed in jet-lag studies and is thought to reflect an influence of circadian rhythmicity on the 24-h profiles [10].

The search for an association between the internal sleep structure and the episodic PRL pulses has led to conflicting reports. A relationship between the alternation of REM and NREM sleep episodes and the occurrence of nadirs and peaks in plasma PRL levels has been described [11], but other studies have failed to find evidence of such an association [9,12]. Using spectral analysis of the sleep EEG, a temporal link between PRL release and EEG has been described, with PRL secretory rates positively correlated with delta wave activity, and negatively with alpha and beta bands (Fig. 2) [13]. Figure 3 illustrates the time course of the mean pulse of PRL secretory rates and of the concomitant delta wave activity. Together with an increase in mean PRL levels, delta wave activity exhibited only a tendency to increase, possibly due to the various time lags between PRL secretory rates and delta wave activity.

PRL secretion is known to be under multifactorial regulation, but the control mechanisms are not yet completely understood. Its secretory regulation is mainly inhibitory, and dopamine (DA) appears to be the principal hypothalamic inhibitory factor, acting directly on the pituitary. DA may be implicated in the regulatory mechanisms of the sleep-wake cycle, playing a prominent role during daytime, but also in sleep structure regulation [14]. Such a role of DA is supported by biochemical and electrophysiological data. Infusion of apomorphine, an agonist of DA receptors, decreases PRL secretion [15] and reduces delta wave activity [14]. It is then questionable whether the parallel time course of PRL secretory rates and delta wave activity could be attributable to a common influence of DA. The mechanisms that subserve coupling between PRL release and slow waves probably involve other neurotransmitters as well, which remain to be identified.

Growth hormone (GH)

The 24-h GH profile is characterized by a sleep-dependent rhythm, with a large secretory episode occurring just after sleep onset, and being temporally related to the first episode of slow-wave sleep (SWS) [16,17]. Other pulses may occur in later sleep and during wakefulness, in the absence of any identifiable stimulus. Figure 1 illustrates the mean GH profiles during a normal 24-h period, and during a 24-h period with an

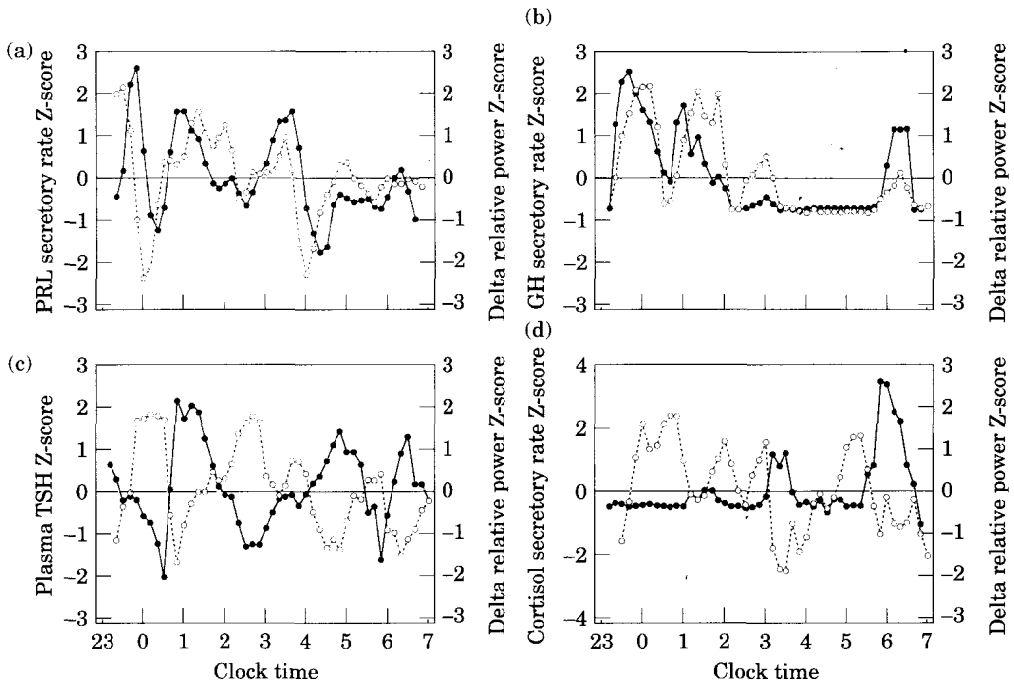


Figure 2. Nocturnal profiles of PRL (a), GH (b), TSH (c) and cortisol (d) (solid) together with the concomitant delta wave activity (dashed). PRL and GH profiles are positively correlated with delta wave activity, whereas TSH and cortisol are negatively correlated with delta wave activity.

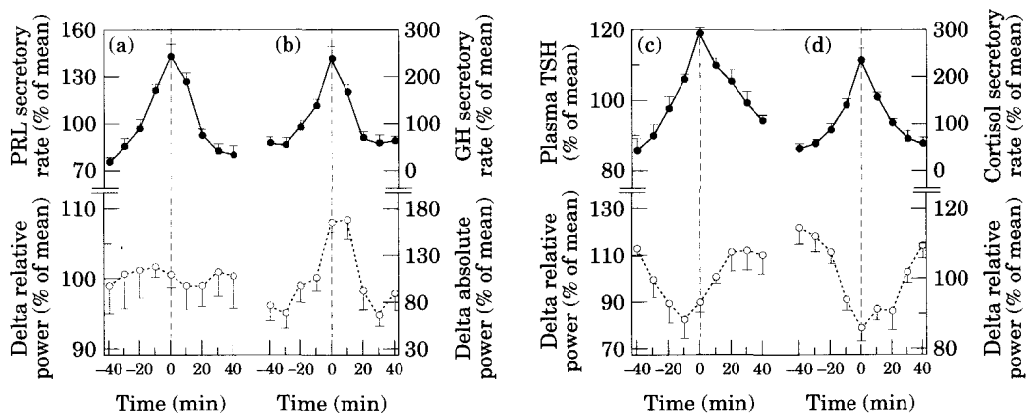


Figure 3. Mean (\pm SE) pulses of cortisol (a), TSH (b), PRL (c); and GH (d) and of concomitant delta wave activity. The time scale (x-axis) represents the time in min, corresponding to the 10-min blood samples, before and after the maximum of the hormonal pulse. Values of hormonal pulses and of delta wave activity are expressed as percentages of the mean individual pulses.

8-h shift in the sleep period. Both during night-time and daytime sleep, a large GH pulse occurred just after sleep onset. As for PRL, significant pulses were observed during the night of sleep deprivation, at the time of habitual sleep, and could be attributable to a circadian influence.

Despite the large number of studies on the subject, the underlying mechanisms coupling GH and SWS have not yet been identified. Some authors have concluded that the temporal association observed between GH pulses and the first episode of SWS may be fortuitous [18,19]. However, in more recent studies, using deconvolution procedure of plasma GH levels, a close association was found between SWS and GH secretory rates [20]. In addition, a significant correlation was found between the amount of GH secreted in the SWS-associated pulses and the duration of SWS occurring during the pulse, under normal conditions [21], as well as after stimulation of SWS with gamma-hydroxybutyrate [22]. This result was confirmed by another study using spectral analysis of the sleep EEG, in which a significant correlation between the GH secretory rates and delta wave activity profiles throughout the night was reported (Figs. 2 and 3), as well as a quantitative relationship between the amount of GH secreted and the concomitant amount of delta wave activity [23]. This relationship was preserved after enrichment of sleep in delta waves by ritanserin, a 5-HT₂ receptor antagonist, and the drug-related increase in delta wave activity was accompanied by a concomitant and proportional increase in GH secretory rates [23]. Similarly, growth hormone-releasing hormone (GHRH) administration has been described as producing a concomitant increase in plasma GH concentrations and in SWS [24] or in theta waves [25]. Similarly, a concomitant decrease in GH levels and in SWS was observed following the administration of corticotropin-releasing hormone (CRH) [26]. Taken together, these results suggest that the regulatory mechanisms involved in the control of delta wave activity and GH secretion are closely linked.

Thyrotropin (TSH)

Thyrotropin (TSH) exhibits a 24-h rhythm generated by amplitude and frequency modulation of secretory pulses [1]. TSH displays low daytime values which begin to increase in the late afternoon, reaching maximum levels around the time of sleep onset. Subsequently, a slow decline, generally attributed to an inhibitory influence by sleep processes, occurs during the night [27,28]. Figure 1 presents the 24-h profiles of TSH both during a normal 24-h period and a sleep shift. During sleep deprivation, TSH levels are clearly enhanced with higher TSH levels occurring later in the night. Thus, it is generally admitted that sleep exerts an inhibitory influence on TSH secretion. The 24-h TSH profile results from an interaction between the endogenous circadian rhythm and a sleep-related inhibitory effect. When the depth of sleep at the habitual time is enhanced by prior sleep deprivation, the nocturnal TSH rise is markedly reduced, suggesting that SWS is probably the primary determinant of the sleep-associated fall [27].

A temporal association has been described between the internal sleep structure and TSH pulses: SWS is associated with declining plasma TSH levels, and awakenings with rising levels [29,30]. These relationships were confirmed using spectral analysis of the sleep EEG, which demonstrated that the whole TSH profile was negatively correlated with the delta wave activity (Fig. 2) [31]. Figure 3 clearly shows that the

mean increase in TSH levels was linked to a mean decrease in delta wave activity, and conversely, the decrease in TSH levels was associated with an increase in delta wave activity. In addition, the alpha slow-wave index (ASI), an estimator of the intra-sleep awakenings [4], and TSH exhibited a significant temporal association [31], which further confirms the previously described association between awakenings and TSH rising levels. From these results, it appears that the nocturnal TSH profile closely reflects variations of sleep EEG activity. However, whether EEG activity has a modulatory role on TSH levels, or inversely, whether TSH variations could influence sleep structure, remains to be clarified.

Much less is known about the origin of TSH pulsatile secretion. A primary role for TRH in controlling TSH release has been suggested by studies showing that pulsatility disappears with hypothalamic lesions [32] and can be restored by repetitive TRH administration [33]. Moreover, functional blocking of TRH receptors have been shown to abolish the TSH pulsatility, suggesting that TSH pulses were linked to those of TRH [34]. The inhibitory control of DA and somatostatin on TRH seems not to play a major role, since their infusion does not alter TSH pulsatility [33]. Despite the current use of TRH stimulation test in thyroid disease or in depression, to our knowledge no studies have challenged the influence of TRH or TSH on sleep in man. Such experiments remain to be carried out in order to better understand the temporal relationships between sleep and TSH pulses, and their underlying mechanisms.

Cortisol

The 24-h cortisol rhythm is generally considered to be mainly under endogenous circadian control. Its pattern is known to be relatively independent of sleep, since it is poorly affected by short-term manipulations of sleep such as sleep reversal, selective and total sleep deprivation, and abrupt shift in the sleep period (Fig. 1). However, temporal relationships between cortisol and sleep have been found, and sleep has been described to exert an inhibitory effect on cortisol release, particularly in the first few hours of the night [35–37]. Nevertheless, other studies have concluded, on the contrary, that sleep does not inhibit cortisol since diurnal sleep failed to suppress cortisol release [38,39].

Despite these discrepancies, temporal relationships between cortisol pulses and the internal sleep structure have been described. Nowadays, it is generally admitted that awakenings or light sleep periods are linked to increasing plasma levels [36,39,40], whereas SWS is associated with low or decreasing cortisol levels [39,40]. Using spectral analysis of the sleep-EEG and deconvolution procedure for estimation of the cortisol secretory rates, we recently described an inverse relationship between cortisol secretory pulses and oscillations in delta wave activity during nocturnal sleep [41] as well as during diurnal sleep [42]. Increases in cortisol secretory rates were associated with decreases in delta wave activity, and conversely, peaks in delta wave activity occurred only during low cortisol secretion (Fig. 2). Both cross-correlation analysis of the two series and mean pulse analysis (Fig. 3) revealed that cortisol changes preceded the changes in EEG activity by about 10 min. In addition, individual pattern analysis shows that up to 90% of ascending phases of cortisol secretory pulses were temporally associated with non-ascending phases of concomitant delta wave activity during sleep. This indicates that cortisol secretion or its secretory processes may modulate the EEG activity, rather than the inverse.

Corticoid administration has been generally described to exert an activating effect on sleep, increasing wakefulness and light sleep, and decreasing SWS [43,44]. However, other studies have reported an enhancing effect, which could seem paradoxical, of glucocorticoids on the amount of SWS [45–47]. Recently, this stimulating effect of cortisol administration on SWS has been attributed to a mechanism that activates pituitary GH release and simultaneously antagonizes the effects of CRH and somatostatin [47]. This is in accordance with an activating effect of the hypothalamo-pituitary axis on sleep EEG, and is not in disagreement with the model of reciprocal interaction of GHRH and CRH in sleep regulation previously described [48,49].

Conclusions

This review highlights the wide variety of relationships between sleep and pituitary activity. As in the case of renin, for which a strong and systematic relationship between nocturnal oscillations and sleep stages has been described [50], for certain pituitary hormones such as prolactin and growth hormone, the occurrence of sleep is a major factor determining the 24-h profile. On the other hand, other hormones such as cortisol have a strong circadian rhythm. TSH lies on the frontier of these classes of hormones, as it is influenced both by sleep and by circadian processes. For all of these hormones, recent studies using new analytical procedures demonstrated temporal links between their secretory pulses and the concomitant variations in EEG activity during sleep. In particular, spectral analysis of the sleep EEG offers a more detailed and dynamic description of the sleep processes than the traditional visual scoring of sleep stages, and allows a quantitative evaluation of the EEG activity, and therefore a quantitative analysis of the relationship between hormonal secretion and delta wave activity [23].

It is tempting to hypothesize that common central mechanisms regulate both EEG activity and hormone release. Coupling mechanisms differ widely among endocrine systems, since delta wave activity is in phase opposition with TSH and cortisol release, and in phase with variations in GH and, to a lesser extent, in PRL. Moreover, the various time-lags observed between the occurrence of delta wave peaks and hormonal pulses give evidence for complex underlying processes. PRL, GH and TSH profiles are rather concomitant with or lagged behind the delta wave activity profile, whereas cortisol secretion and thereby ACTH, preceded variations in delta wave activity, which appears to be interpreted as a permissive effect by low cortisol on delta wave activity. That other groups have found an increase in SWS duration following exogenous cortisol administration does not appear to be contradictory. Indeed, the hypothesis that exogenous cortisol inhibits endogenous release of CRH and stimulates GHRH and consequently increases SWS, could reconcile the two observations.

Knowledge concerning the persistence of the temporal relationships between sleep and hormonal secretion in disease states are fragmentary. In pathologies involving both sleep and endocrine symptoms, it is difficult to know to what extent sleep degradation modifies endocrine systems or, conversely, if hormonal perturbations induce sleep disturbances. Similarly, little is known about the physiological significance and the clinical implications of the described relationships. For example, it has been shown that in human African trypanosomiasis (sleeping sickness), there are profound modifications in the temporal organization of the 24-h hormone profiles, together with the disruption of the sleep-wake cycle. Still, despite such alterations, the temporal relationships between hormone pulses and specific sleep stages remain persistent [50].

Similarly, the circadian system has been shown to adapt only partially in night workers, without any disturbances in the relationships between hormonal release and the internal sleep structure.⁵² These results emphasize the strength of the coupling processes and their independence from the circadian timing system. However, new data are needed to determine whether the maintenance of normal sleep-associated endocrine events should be considered to be an important criterion in health problems.

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